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Hypertension. 2014;63:222-228; originally published online November 18, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01940

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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<http://hyper.ahajournals.org/content/63/2/222>

Data Supplement (unedited) at:

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Association of Target Organ Damage With 24-Hour Systolic and Diastolic Blood Pressure Levels and Hypertension Subtypes in Untreated Chinese

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Abstract—The association of target organ damage with 24-hour systolic and diastolic blood pressure levels and ambulatory hypertension subtypes has not yet been examined in untreated Chinese patients. We measured left ventricular mass index by echocardiography (n=619), the urinary albumin:creatinine ratio (n=1047), and aortic pulse wave velocity by tonometry (n=1013) in 1047 untreated subjects (mean age, 50.6 years; 48.9% women). Normotension was a 24-hour systolic/diastolic blood pressure <130/<80 mmHg. Hypertension subtypes were isolated diastolic hypertension and mixed systolic plus diastolic hypertension. We assessed associations of interest by multivariable-adjusted linear models. Using normotension as reference, mixed hypertension was associated with higher ($P \leq 0.003$) left ventricular mass index (+4.31 g/m²), urinary albumin:creatinine ratio (+1.63 mg/mmol), and pulse wave velocity (+0.76 m/s); and isolated diastolic hypertension was associated with similar left ventricular mass index and pulse wave velocity ($P \geq 0.39$), but higher urinary albumin:creatinine ratio (+1.24 mg/mmol; $P = 0.002$). In younger participants (<55 years), the mutually independent effect sizes associated with 1 SD increases in 24-hour systolic/diastolic blood pressure were +3.31/−0.36 g/m² ($P = 0.009/0.79$) for left ventricular mass index, +1.15/+1.14 mg/mmol ($P = 0.02/0.04$) for the urinary albumin:creatinine ratio, and +0.54/−0.05 m/s ($P < 0.001/0.54$) for pulse wave velocity. In older participants, these estimates were +3.58/+0.30 g/m² ($P = 0.045/0.88$), +1.23/+1.05 mg/mmol ($P = 0.002/0.54$), and +0.76/−0.49 m/s ($P < 0.001/0.001$), respectively. In conclusion, 24-hour systolic blood pressure and mixed hypertension are major determinants of target organ damage irrespective of age and target organ, whereas 24-hour diastolic blood pressure and isolated diastolic hypertension only relate to the urinary albumin:creatinine ratio below middle age. (*Hypertension*. 2014;63:222–228.) • **Online Data Supplement**

Key Words: blood pressure monitoring, ambulatory ■ hypertrophy, left ventricular ■ vascular stiffness

Hypertension remains the predominant driver of cardiovascular disease. In 2001, hypertension caused 8 million deaths worldwide, representing 14% of global mortality.¹ In the early intervention trials in hypertension,^{2,3} patients were selected based on diastolic blood pressure. However, the Framingham investigators^{4,5} and others⁶ showed in studies published as early as 1971 that diastolic blood pressure was the strongest predictor of cardiovascular outcome below age 50 years with a matching increase in the importance of systolic blood pressure at higher age. These epidemiological observations contradicted the long-held view that diastolic blood pressure might be a better predictor of risk because it reflects the resistance the heart must overcome to eject blood.⁷

Using blood pressure levels of 140 mmHg systolic and 90 mmHg diastolic, current guidelines subdivide hypertension into isolated diastolic, isolated systolic, and diastolic

combined with systolic (mixed) hypertension. Studies in Asian cohorts demonstrated that isolated diastolic hypertension confers a cardiovascular risk that is intermediate between the risks associated with normotension and isolated systolic or mixed hypertension, but they were based on office blood pressure.^{8,9} Ambulatory blood pressure monitoring substantially refines risk stratification.¹⁰ To our knowledge, no previous study applied ambulatory monitoring in Chinese patients to examine target organ damage in relation to isolated diastolic or mixed hypertension or examined the age dependency of the association of systolic versus diastolic blood pressure as independent correlates of target organ damage. We addressed these issues in a cross-sectional analysis of 1047 untreated Chinese patients referred for ambulatory blood pressure monitoring to the Hypertension Department of Ruijin Hospital in Shanghai.

Received June 27, 2013; first decision July 11, 2013; revision accepted October 22, 2013.

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This paper was sent to David A. Calhoun, Guest editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at <http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.01940/-DC1>.

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.113.01940

Methods

Study Population

As described elsewhere,^{11,12} we recruited consecutive patients referred for ambulatory blood pressure monitoring to the Hypertension Outpatient Clinic of Ruijin Hospital, Shanghai, China. We adhered to the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine. Of those referred between December 2008 and December 2012, a total of 2159 patients were eligible because they were either never treated or had discontinued their blood pressure-lowering drugs for ≥ 2 weeks. Of those, 1281 patients (59.5%) gave informed written consent. We excluded 234 participants from analysis (for details, see the online-only Data Supplement). Thus, the number of participants analyzed totaled 1047. Among those analyzed, left ventricular mass index was measured in 619 participants, the urinary albumin:creatinine ratio in 1047 participants, and aortic pulse wave velocity was measured in 1013 participants.

Blood Pressure Measurement

We programmed validated oscillometric SpaceLabs 90217 monitors (SpaceLabs, Redmond, WA) to obtain blood pressure readings at 20-minute intervals during daytime (06:00–22:00) and at 30-minute intervals during nighttime (22:00–06:00). All recordings covered >20 hours and included $\geq 70\%$ of the programmed readings. The 24-hour, daytime and nighttime blood pressure means were weighted for the time interval between consecutive readings (for the computing formula, see the online-only Data Supplement). Ambulatory hypertension was a 24-hour blood pressure of ≥ 130 mmHg systolic or 80 mmHg diastolic. The thresholds for daytime blood pressure were 135 mmHg systolic and 85 mmHg diastolic, and for nighttime 120 and 70 mmHg, respectively.

On the day of the completion of the 24-hour ambulatory blood pressure monitoring, office blood pressure was measured using the Omron HEM-7051 device (Omron HealthCare, Kyoto, Japan). After the participants had rested in the sitting position for ≥ 10 minutes, 3 consecutive blood pressure readings were obtained according to the recommendations of the European Society of Hypertension.¹⁰ For analysis, the 3 readings were averaged. Office hypertension was a blood pressure of ≥ 140 mmHg systolic or 90 mmHg diastolic.

Using abovementioned thresholds, white-coat hypertension was defined as a raised office blood pressure in the presence of a normal 24-hour blood pressure. Masked hypertension was an elevated 24-hour ambulatory blood pressure with normal office blood pressure and sustained hypertension a consistently elevated blood pressure on both office and ambulatory measurement.

Assessment of Target Organ Damage

Trained observers ($n=2$) did the arterial measurements, using a high-fidelity SPC-301 micromanometer (Millar Instruments, Houston, TX) interfaced with a laptop computer, running the SphygmoCor software version 7.1 (AtCor Medical, West Ryde, New South Wales, Australia). Aortic pulse wave velocity was measured by sequential ECG-gated recordings of the arterial pressure waveform at the carotid and femoral arteries. Distances from the suprasternal notch to the carotid sampling site (distance A) and from the suprasternal notch to the femoral sampling site (distance B) were measured. Pulse wave travel distance was distance B minus distance A. Pulse transit time was the average of 10 consecutive beats. Pulse wave velocity was the distance in meters divided by the transit time in seconds.

Two experienced observers (T.-Y.X. and F.-H.D.) performed all echocardiograms according to the recommendations of the American Society of Echocardiography, using a Phillips IE33 device (Phillips, Eindhoven, The Netherlands) interfaced with a 2.5-MHz phased-array probe. For details of the determination of left ventricular mass index, see the online-only Data Supplement.

Venous blood samples, collected after overnight fasting, were analyzed by automated enzymatic methods for serum cholesterol and uric acid and plasma glucose. Diabetes mellitus was a plasma glucose level of ≥ 7.0 mmol/L or use of antidiabetic drugs.¹³ A first-morning

urine sample was collected for the measurement of the urinary albumin (in milligram) and creatinine (in millimoles) concentrations.

Other Measurements

Nurses administered a standardized questionnaire to inquire about each participant's medical history, intake of medications, and smoking and drinking habits. They measured body height and waist circumference to the nearest 0.5 cm. Participants wore light indoor clothing without shoes for body weight measurement. Body mass index was weight in kilograms divided by the height in meters squared.

Statistical Analysis

For database management and statistical analysis, we used the Statistical Analysis System (SAS), version 9.3 (SAS Institute, Cary, NC). Departure from normality was evaluated by Shapiro-Wilk statistic. We normalized the distribution of the urinary albumin:creatinine ratio by a logarithmic transformation. For comparison of means and proportions, we applied the analysis of variance and the χ^2 -statistic, respectively. We determined differences in target organ damage between normotension, isolated diastolic hypertension, and mixed hypertension from generalized linear models as implemented in the PROC GLM procedure in the SAS software package. As covariables, we considered sex, age, body mass index, 24-hour heart rate, plasma glucose, serum cholesterol, and smoking and drinking. After stratification for age (<55 versus ≥ 55 years), we applied multiple linear regression to determine the effect sizes of target organ damage associated with 1-SD increase in ambulatory systolic and diastolic blood pressure levels. We compared effect sizes between subgroups, using the appropriate interaction terms. We computed the variance inflation factor to assess to what extent parameter estimates for systolic and diastolic blood pressure levels were affected by collinearity in regression models including both blood pressure components.

Results

Baseline Characteristics

The primary reason for referral to 24-hour ambulatory blood pressure monitoring was diagnosis of blood pressure status in 968 (92.4%) never-treated participants or confirmation of the indication for antihypertensive drug treatment in 79 (7.6%) previously treated patients after ≥ 2 weeks of discontinuation of blood pressure-lowering agents. The median number of readings averaged to estimate the 24-hour blood pressure was 60 (5th–95th percentile interval, 48–64; range, 45–67). Of the 1047 participants, 412 (39.4%), 283 (27.0%), and 352 (33.6%) participants were normotensive or had isolated diastolic hypertension or mixed hypertension on 24-hour ambulatory measurement, respectively. The study population included 512 women (48.9%) and 310 (29.6%) patients with office hypertension. Age averaged (\pm SD) 50.6 ± 10.4 years. Among women, the prevalence of smoking and drinking was 0.6% and 6.6%, and among men 36.6% and 35.7%, respectively.

Table 1 shows the baseline characteristics of the participants by categories of the 24-hour ambulatory blood pressure. Patients with ambulatory hypertension were more likely to be male, to smoke, and to drink alcohol, and had higher body mass index, waist circumference, and serum uric acid ($P \leq 0.012$ for all). Among participants with 24-hour ambulatory normotension, 88.6% of participants were also normotensive on office measurement, and 11.4% of participants had white-coat hypertension. Among patients with 24-hour isolated diastolic hypertension, the prevalence of masked and sustained diastolic hypertension was 77.0% and 23.0%,

Table 1. Characteristics of Participants

Characteristics	Normotension	Isolated Diastolic Hypertension	Mixed Systolic and Diastolic Hypertension
Number of subjects (%)	412 (39.4)	283 (27.0)	352 (33.6)
Women	268 (65.1)	115 (40.6)	129 (36.7)
Smokers	49 (11.9)	55 (19.4)	95 (27.0)
Drinking alcohol	46 (11.2)	82 (29.0)	97 (27.6)
Diabetes mellitus	22 (5.3)	11 (3.9)	14 (4.0)
Never treated for hypertension	383 (93.0)	257 (90.8)	328 (93.2)
Mean characteristic (SD)			
Age, y	54.4±10.2	47.8±9.5	48.4±10.0
Waist circumference, cm	85.9±9.0	88.6±8.9	90.1±8.7
Body mass index, kg/m ²	23.9±3.2	24.5±3.0	25.1±2.8
Conventional blood pressure			
Systolic, mm Hg	123.8±13.3	127.7±9.7	140.3±13.3
Diastolic, mm Hg	74.0±8.4	83.3±6.9	87.7±8.6
Heart rate, bpm	72.0±10.0	75.3±9.8	74.0±9.8
24-h blood pressure			
Systolic, mm Hg	116.4±7.4	124.2±4.1	139.8±7.8
Diastolic, mm Hg	73.1±5.0	84.6±3.4	90.8±6.4
Heart rate, bpm	70.4±7.5	74.5±7.3	74.7±7.9
Plasma glucose, mmol/L	5.10±0.83	4.98±0.75	5.17±0.98
Serum total cholesterol, mmol/L	5.05±0.87	4.96±0.92	4.99±0.85
Uric acid, μmol/L	300.5±77.7	326.4±79.5	333.9±93.1

Hypertension was a 24-h ambulatory blood pressure of ≥ 130 mm Hg systolic or 80 mm Hg diastolic. All differences with the normotensive group were significant ($P \leq 0.012$) with the exception of plasma glucose ($P \geq 0.083$), serum cholesterol ($P \geq 0.19$), the prevalence of diabetes mellitus ($P \geq 0.38$) and number of subjects never treated for hypertension ($P \geq 0.30$). To convert cholesterol, glucose and uric acid from mmol/L to mg/dL, multiply by 38.6, 18.0, and 0.0168, respectively. BPM indicates beats per minute.

respectively. Among patients with 24-hour systolic and diastolic hypertension, the prevalence of masked and sustained hypertension was 43.8% and 56.2%, respectively.

Target Organ Damage by Categories of Ambulatory Hypertension

In multivariable-adjusted analyses (Table 2), patients with mixed hypertension had higher ($P \leq 0.009$) left ventricular mass index, urinary albumin:creatinine ratio, and pulse wave velocity than normotensive individuals. As shown in the Figure, the increases amounted to +4.31 g/m², +1.63 mg/mmol, and +0.76 m/s, respectively. Patients with isolated diastolic hypertension compared with normotensive subjects had similar left ventricular mass index and pulse wave velocity ($P \geq 0.39$), but higher ($P = 0.002$) urinary albumin:creatinine ratio. The differences with the normotensive group were +0.15 g/m², +1.24 mg/mmol, and +0.09 m/s (Figure). Trends in women and men were similar ($P \geq 0.15$ for interaction; Table 2). Sensitivity analyses from which we excluded previously treated patients (Table S1 in the online-only Data Supplement) or based on daytime (Table S2) or nighttime (Table S3) blood pressure were confirmatory.

Effect Sizes Associated With Ambulatory Systolic and Diastolic Blood Pressures

In line with previous publications based on the conventionally measured blood pressure,⁴⁻⁶ we stratified our

multivariable-adjusted analyses of 24-hour systolic and diastolic blood pressure levels as continuous risk indicators by age (< 55 versus ≥ 55 years). In younger participants (Table 3), a 1-SD increase in the 24-hour diastolic blood pressure was significantly associated with higher albumin:creatinine ratio (+1.14 mg/mmol; $P = 0.04$) in fully adjusted models. Independent of diastolic blood pressure, a 1-SD increase in the 24-hour systolic blood pressure was associated with higher left ventricular mass index (+3.31 g/m²; $P = 0.009$), higher pulse wave velocity (+0.54 m/s; $P < 0.001$), and an increased albumin:creatinine ratio (+1.15 mg/mmol; $P = 0.02$).

In older participants (Table 3), the 24-hour diastolic blood pressure was not positively associated with any measure of target organ damage independent of systolic blood pressure ($P \geq 0.54$) and was negatively associated with pulse wave velocity (−0.49 m/s; $P < 0.001$); in fully adjusted models, a 1-SD increase in the 24-hour systolic blood pressure was associated with higher left ventricular mass index (+3.58 g/m²; $P = 0.045$), higher albumin:creatinine ratio (+1.23 mg/mmol; $P = 0.002$), and higher pulse wave velocity (+0.76 m/s; $P < 0.001$). In all fully adjusted models, the variance inflation factors for systolic and diastolic blood pressure levels did not exceed 4.24. The age-by-blood pressure interaction terms were nonsignificant for 24-hour systolic ($P \geq 0.12$) and diastolic ($P \geq 0.47$) blood pressure levels except for 24-hour diastolic blood pressure in relation to pulse wave velocity ($P = 0.01$).

Table 2. Multivariable-Adjusted Indexes of Target Organ Damage by Hypertension Category

Measure of Target Organ	Normotension	Isolated Diastolic Hypertension	Mixed Systolic and Diastolic Hypertension
Women			
Left ventricular mass index, g/m ²	88.8±15.4 (n=165)	86.9±15.7 (n=62)	93.5±14.7 (n=75)
Albumin:creatinine ratio, mg/mmol	0.57 (0.11–2.85) (n=268)	0.76 (0.14–4.12)* (n=115)	0.95 (0.20–4.56)† (n=129)
Pulse wave velocity, m/s	7.5±1.3 (n=259)	7.5±1.3 (n=111)	8.4±1.2† (n=127)
Men			
Left ventricular mass index, g/m ²	91.7±14.3 (n=80)	93.9±14.4 (n=92)	96.5±14.4* (n=145)
Albumin:creatinine ratio, mg/mmol	0.38 (0.07–1.97) (n=144)	0.44 (0.09–2.01) (n=168)	0.59 (0.14–2.59)† (n=223)
Pulse wave velocity, m/s	7.5±1.2 (n=139)	7.6±1.1 (n=162)	8.1±1.2† (n=215)
All participants			
Left ventricular mass index, g/m ²	90.5±15.7 (n=245)	90.7±14.9 (n=154)	94.8±14.8‡ (n=220)
Albumin:creatinine ratio, mg/mmol	0.46 (0.09–2.24) (n=412)	0.57 (0.11–2.96)‡ (n=283)	0.75 (0.17–3.25)† (n=352)
Pulse wave velocity, m/s	7.5±1.2 (n=398)	7.6±1.2 (n=273)	8.2±1.3† (n=342)

Values are mean±SD or geometric mean (5th–95th percentile interval). Reported values are standardized to the mean distribution in all participants of sex (if applicable), age, body mass index, 24-h heart rate, plasma glucose, serum cholesterol, and smoking and drinking. Hypertension was a 24-h ambulatory blood pressure of ≥130 mm Hg systolic or 80 mm Hg diastolic. n indicates the number of participants with measurements available in each subgroup.

Significance of the differences with normotension: * $P \leq 0.05$, † $P \leq 0.001$, and ‡ $P \leq 0.01$.

Discussion

We studied the associations of 24-hour systolic and diastolic blood pressure levels and distinct types of ambulatory hypertension with intermediate signs of target organ damage in referred subjects, of whom all were untreated for ≥ 2 weeks, and $\approx 90\%$ of the subjects had never been treated. The key findings were that left ventricular mass index, the urinary albumin:creatinine ratio, and aortic pulse wave velocity increased with 24-hour systolic blood pressure, irrespective of age group and independent of diastolic blood pressure. The albumin:creatinine ratio increased with the 24-hour diastolic blood pressure, independent of systolic blood pressure, but only in younger participants. Furthermore, in categorical

analyses and compared with normotension, all studied indices indicated more severe target organ damage in patients with systolic combined with diastolic hypertension, whereas isolated diastolic hypertension was only associated with a higher albumin:creatinine ratio.

Two subject-level meta-analyses^{14,15} addressed the association between cardiovascular mortality and systolic versus diastolic blood pressure in people with no previous vascular disease at enrolment. The Prospective Studies Collaboration¹⁴ reported that among 1 million people there was a log-linear relation between the risk of vascular death and blood pressure down to levels as low as 115 mmHg systolic and 75 mmHg diastolic. This association was consistent throughout decades

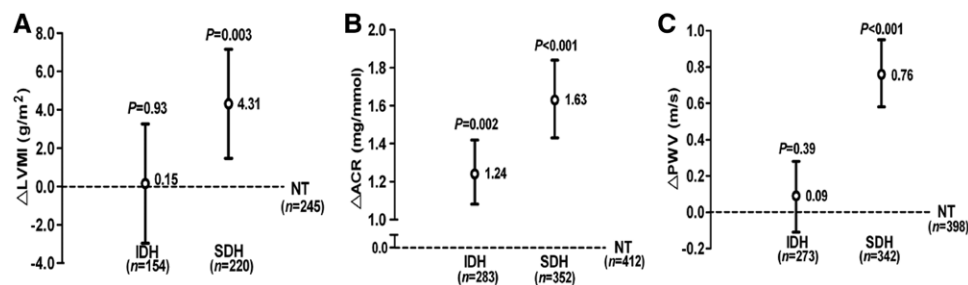


Figure. Differences (Δ) in left ventricular mass index (LVMI; **A**), the albumin:creatinine ratio (ACR; **B**), and pulse wave velocity (PWV; **C**) between normotensive (NT) subjects and patients with isolated diastolic hypertension (IDH) or mixed systolic and diastolic hypertension (SDH). The dotted lines indicate zero difference with the reference group. Differences are means adjusted for sex, age, body mass index, 24-hour heart rate, plasma glucose, serum cholesterol, and smoking and drinking. Vertical bars indicate the 95% confidence interval. The number of participants contributing to each statistical estimate is given. Because ACR was analyzed on a logarithmic scale, Δ ACR is the ratio of the hypertensive versus the normotensive group.

Table 3. Multivariable-Adjusted Standardized Regression Coefficients With 24-Hour Systolic and Diastolic Blood Pressure Levels by Age Groups

Measure of Target Organ	<55 y		≥55 y	
	Diastolic Pressure	Systolic Pressure	Diastolic Pressure	Systolic Pressure
Left ventricular mass index, g/m ²				
No.	394		225	
A	2.70±0.72*	3.03±0.66*	3.32±1.39†	3.78±1.20‡
FA	−0.36±1.37	3.31±1.26‡	0.30±2.04	3.58±1.78†
Albumin:creatinine ratio, mg/mmol				
No.	658		389	
A	1.30 (1.20–1.40)*	1.27 (1.20–1.35)*	1.26 (1.14–1.39)*	1.27 (1.18–1.37)*
FA	1.14 (0.99–1.31)†	1.15 (1.02–1.29)†	1.05 (0.90–1.23)	1.23 (1.08–1.42)‡
Pulse wave velocity, m/s				
No.	634		379	
A	0.44±0.05*	0.50±0.05*	0.17±0.08†	0.45±0.07*
FA	−0.05±0.09	0.54±0.08*	−0.49±0.12*	0.76±0.10*

Regression coefficients±SE or (95% confidence interval) express the risk associated with a 1-SD increase in 24-h systolic (12.1 mm Hg) or diastolic (9.3 mm Hg) blood pressure levels. All models were adjusted for sex, age, body mass index, 24-h heart rate, plasma glucose, serum cholesterol, and smoking and drinking. Adjusted models (A) include either systolic or diastolic blood pressure, whereas fully adjusted models (FA) include both systolic and diastolic blood pressure levels in addition to the aforementioned covariables. No. indicates the number of participants contributing to the estimates.

Significance of the regression coefficients: * $P \leq 0.001$, † $P \leq 0.05$, and ‡ $P \leq 0.01$.

of life, ranging from middle (40–49 years) to old age (80–89 years). The informativeness of systolic and diastolic blood pressure levels for the prediction of stroke was similar (89% versus 83%), although systolic blood pressure was superior to diastolic blood pressure for the prediction of ischemic heart disease (93% versus 73%).¹⁴ The Asia Pacific Cohort Studies Collaboration¹⁵ also reported a log-linear relation between cardiovascular mortality and blood pressure. The strength of the associations of mortality from stroke and ischemic heart disease with systolic and diastolic blood pressure was similar.¹⁴ In a more recent publication,⁹ the Asia Pacific Cohort Studies Collaboration reported that the multivariable-adjusted hazard ratios of cardiovascular mortality associated with isolated diastolic hypertension and combined hypertension in comparison with normotension were 1.81 (95% confidence interval, 1.61–2.04) and 3.42 (3.17–3.70), respectively ($P < 0.001$ for the difference). The Framingham investigators^{4,5} were the first to consider age as a modulator of the risk associated with systolic and diastolic blood pressure levels. In 2001, Franklin et al⁵ demonstrated that with increasing age, there was a gradual shift from diastolic to systolic blood pressure and then to pulse pressure as predictors of coronary heart disease. In subjects <50 years, diastolic blood pressure was the strongest predictor. Age 50 to 59 years was a transition period when all 3 blood pressure indexes were comparable predictors, and from 60 years of age onward, diastolic blood pressure was negatively related to the risk of coronary heart disease so that pulse pressure became superior to systolic blood pressure.⁵

Bliziotis et al¹⁶ did a meta-analysis of summary statistics from 14 studies (n=2485) assessing echocardiographic left ventricular mass index in relation to systolic/diastolic blood pressure. The pooled correlation coefficients were 0.23/0.19, 0.37/0.26, and 0.46/0.28 for office, 24-hour ambulatory, and home blood pressure levels. The difference between the

systolic and diastolic correlation coefficients was significant ($P < 0.001$) for home blood pressure but was not reported for office and 24-hour ambulatory blood pressure levels.¹⁶ Cui et al¹⁷ did a retrospective survey and collected data from computerized medical files of 17 682 patients with essential hypertension, ≥ 60 years old, and hospitalized in Beijing from January of 1993 to December of 2008. Target organ damage in this Chinese study was cerebrovascular disease, coronary heart disease, chronic kidney disease, or aortic dissection. Patients with target organ damage had higher systolic blood pressure, whereas there was no significant difference in diastolic blood pressure. In multivariable-adjusted logistic regression, cerebrovascular disease (odds ratio, 1.18), coronary heart disease (2.41), chronic kidney disease (1.36), or aortic dissection (2.18) showed significant association with systolic blood pressure, whereas the corresponding associations with diastolic blood pressure were nonsignificant.¹⁷

Few publications addressed the association between the urinary albumin:creatinine ratio and blood pressure components or hypertension subtypes. Lin et al¹⁸ recruited subjects with normal blood pressure (n=41), isolated diastolic hypertension (n=52), or combined systolic and diastolic hypertension (n=31) on 24-hour ambulatory measurement. The prevalence of proteinuria (≥100 mg/dL) was increased from normotension to isolated diastolic hypertension onto combined hypertension (4.9% versus 13.5% versus 19.4%). Drawbacks of this Chinese study were that the thresholds of the 24-hour blood pressure (≥140/≥90 mm Hg) were higher than currently recommended, and that the measurement of proteinuria by dipstick was semi-quantitative. In 1994, Redon et al¹⁹ reported on 95 never-treated patients with essential hypertension, who had 24-hour microalbuminuria measured twice on separate days. Microalbuminuria (30–300 mg) occurred in 26% of patients and, as in our study, was independently associated with higher diastolic blood

pressure (odds ratio per 5 mmHg, 1.09; $P=0.02$).¹⁹ In a subsequent study, Redon et al²⁰ followed 187 patients with essential hypertension at annual intervals for 2.7 years. Initially, all patients were normo-albuminuric and had never been treated for hypertension. Treatment was started after enrollment. With adjustments applied for sex, age, and treatment status, the slope of microalbuminuria over time was associated with the corresponding slope in blood pressure with no difference between systolic and diastolic blood pressure levels.²⁰ With adjustments for the baseline value of microalbuminuria and covariables, the annual increase in systolic blood pressure was associated with higher risk for incident microalbuminuria (hazard ratio for each mmHg per year increase, 1.11; $P<0.01$).²⁰

Aortic pulse wave velocity is the standard measure to quantify arterial stiffness.²¹ The association between pulse wave velocity and systolic blood pressure across the age range is not unexpected. Indeed, higher systolic blood pressure initiates a vicious circle because it is both the cause and consequence of arterial stiffening.^{22,23} Previous studies in patients with hypertension^{23,24} reported that blood pressure as a continuous variable,²⁴ or hypertension on conventional^{23,24} or ambulatory²⁴ measurement predicted thickening of the carotid intima media²⁴ or an increase in aortic pulse wave velocity.²³ Diastolic blood pressure reflects the resistance the heart must overcome to eject blood.⁷ Increase in diastolic blood pressure therefore reflects peripheral arterial resistance, which in turn might move reflection sites of the forward blood pressure wave to more proximal locations, so that the reflected waves return faster, thereby augmenting central systolic blood pressure.²⁵

The current study must be interpreted within the context of its potential limitations and strengths. First, the number of patients with isolated systolic hypertension was too small to allow a meaningful analysis. Therefore, we had to exclude them from analysis. Second, our participants were not representative for a general Chinese population, and our results cannot be extrapolated to other ethnicities. On the contrary, to the best of our knowledge, our current study is the first to report on the association of intermediate signs of target organ damage with systolic and diastolic blood pressure levels and isolated diastolic blood pressure in untreated Chinese, and it extends the findings of previous studies performed in white Europeans or Americans. We assessed blood pressure by 24-hour ambulatory monitoring, which according to current guidelines is state of the art.¹⁰ We did not run analyses based on office blood pressure because 24-hour ambulatory blood pressure substantially refines risk stratification over and beyond office blood pressure²⁶ and because the prevalence of office hypertension in this cohort was only 29.6%. We checked our fully adjusted models for collinearity. There are no formal criteria for deciding whether the variance inflation factor is large enough to affect the predicted values. According to statistical experts,²⁷ variance inflation values >10 indicate collinearity among the predictor variables that warrants corrective action. In all our models, the variance inflation factor between systolic and diastolic blood pressure levels did not exceed 4.24. Finally, the present study had a cross-sectional design and assessed only intermediate signs of target organ damage. Our current findings can therefore not be extrapolated to the incidence of hard cardiovascular or renal end points.

Perspectives

From a clinical point of view, our current study highlights the necessity to treat both systolic and diastolic hypertension to target in particular at younger age when the prevalence of isolated diastolic hypertension and combined hypertension is higher than in the elderly, among whom isolated systolic hypertension is more prevalent.²² According to statistics generated by the International Collaborative Study of Cardiovascular Disease in Asia performed in 2000 to 2001,²⁸ 27.2% of the Chinese adult population aged 35 to 74 years, representing 129 824 000 patients, had hypertension on conventional blood pressure measurement ($\geq 140/\geq 90$ mmHg). Among patients with hypertension, only 44.7% of patients were aware of their high blood pressure, 28.2% were taking antihypertensive medication, and 8.1% of patients achieved blood pressure control ($<140/<90$ mmHg). These results²⁸ along with our current findings underscore the need to develop strategies not only in China²⁸ but worldwide²⁹ to improve prevention, detection, and treatment of hypertension, including isolated diastolic hypertension.

Acknowledgments

We gratefully acknowledge the voluntary participation of all study participants and the expert technical assistance of Jing-Ling Han, Jie Wang, Li Zheng, Yi Zhou, and Wei-Zhong Zhang (The Shanghai Institute of Hypertension, Shanghai, China).

Sources of Funding

This study was supported by grants from the National Natural Science Foundation of China (grants 30871360, 30871081, 81170245, and 81270373); the Ministry of Science and Technology (a grant for China-European Union collaborations [1012]) and the Ministry of Education (NCET-09-0544), Beijing, China; the Shanghai Commissions of Science and Technology (the Rising Star program 11QH1402000) and Education (the Dawn project 08SG20); the Shanghai Bureau of Health (XBR2011004); and the Shanghai Jiaotong University School of Medicine (a grant of Distinguished Young Investigators to Yan Li).

Disclosures

None.

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Novelty and Significance

What Is New?

- This study examined for the first time in referred but untreated Chinese the association of target organ damage with 24-hour systolic and diastolic blood pressure and ambulatory hypertension subtypes. Indexes of target organ damage were left ventricular mass index, the urinary albumin:creatinine ratio, and aortic pulse wave velocity.

What Is Relevant?

- Using normotension as reference, mixed systolic plus diastolic hypertension was associated with higher values of all indexes of target organ damage, whereas isolated diastolic hypertension was associated only with higher albumin:creatinine ratio.
- Higher 24-hour systolic blood pressure was associated with increased target organ damage, irrespective of age.

- Higher 24-hour diastolic blood pressure was associated with increased albumin:creatinine ratio <55 years of age, whereas from 55 years onward higher 24-hour diastolic blood pressure was not positively associated with any index of target organ damage.

Summary

In untreated Chinese patients, 24-hour systolic blood pressure and mixed hypertension are major determinants of target organ damage, irrespective of age and target organ, whereas 24-hour diastolic blood pressure and isolated diastolic hypertension only relate to albumin:creatinine ratio <55 years of age. Our study highlights the necessity to treat both systolic and diastolic hypertension to target.

HYPERTENSION

Expanded Methods and Data Supplement

This Data Supplement has been provided by the authors to give readers additional information about their work.

Supplement to:

Wei F-F *et al.* Association of Target Organ Damage with 24-Hour Systolic and Diastolic Blood Pressure and Hypertension Subtypes in Untreated Chinese.

Expanded Methods

Study Population

We excluded 234 participants from analysis, because their ambulatory blood pressure recording was not kept on file (n=24) or had less than 70% of valid readings (n=35), because their anthropometric (n=55) or biochemical (n=65) characteristics had not been measured, because their drinking or smoking habits had not been recorded (n=2), or because they had measurements more than 3 standard deviations higher than the mean (n=6). Because of the small sample size, we also removed patients with isolated systolic hypertension from the analysis (n=47).

Blood Pressure Measurement

The 24-hour, daytime and nighttime blood pressure means were weighted for the time interval between consecutive readings, according to the following formula:

$$\bar{X} = \sum_{i=1}^n w_i x_i$$

Each blood pressure value is multiplied by a weight that is proportional to the time interval between the preceding and the current reading. The sum of the weights is set to 1. This procedure gives greater weight to readings that cover a longer as compared to smaller time intervals.

Assessment of Target Organ Damage

Two experienced observers (T.-Y.X., F.-H.D.) performed all echocardiograms according to the recommendations of the American Society of Echocardiography, using a Phillips IE33 device (Phillips, Eindhoven, Netherlands) interfaced with a 2.5 MHz phased-array probe. The observers obtained M-mode echocardiograms of the left ventricle from the parasternal long-axis view. All recordings were digitally stored for off-line analysis. We measured left ventricular internal diameter (LVID), interventricular septum (IVS) and posterior wall thickness (PWT) from the M mode image. All measurements were made by the leading-edge method and averaged over 3 cardiac cycles. Mean wall thickness (MWT) was the sum of IVS and PWT at end-diastole divided by two. We computed left ventricular mass in grams from a validated formula as $0.8 \times (1.04 \times [(LVID + IVS + PWT)^3 - LVID^3]) + 0.6$. Left ventricular mass index was left ventricular mass divided by body surface area, calculated as $\text{body weight}^{0.425} (\text{in kg}) \times \text{body height}^{0.725} (\text{in cm}) \times 0.007184$.

Table S1. Multivariable-Adjusted Indices of Target Organ Damage by Hypertension Category in Never-Treated Participants

Measure of Target organ	Normotension	Isolated Diastolic Hypertension	Mixed Systolic and Diastolic Hypertension
Women			
Left ventricular mass index, g/m ²	88.3±14.9 (n=154)	86.9±15.6 (n=55)	93.0±15.0 (n=69)
Albumin-to-creatinine ratio, mg/mmol	0.57 (0.12–2.69) (n=248)	0.74 (0.13–4.32)* (n=100)	0.95 (0.17–5.23)‡ (n=118)
Pulse wave velocity, m/s	7.5±1.2 (n=239)	7.6±1.3 (n=97)	8.4±1.3‡ (n=117)
Men			
Left ventricular mass index, g/m ²	91.5±13.9 (n=76)	94.1±13.8 (n=85)	96.2±14.0 (n=137)
Albumin-to-creatinine ratio, mg/mmol	0.37 (0.08–1.82) (n=135)	0.44 (0.08–2.50) (n=157)	0.61 (0.11–3.34)‡ (n=210)
Pulse wave velocity, m/s	7.4±1.1 (n=130)	7.5±1.1 (n=151)	8.1±1.1‡ (n=202)
All participants			
Left ventricular mass index, g/m ²	90.1±15.2 (n=230)	90.9±14.2 (n=140)	94.5±14.4† (n=206)
Albumin-to-creatinine ratio, mg/mmol	0.45 (0.10–2.09) (n=383)	0.57 (0.12–2.71)† (n=257)	0.76 (0.13–4.50)‡ (n=328)
Pulse wave velocity, m/s	7.5±1.2 (n=369)	7.6±1.3 (n=248)	8.2±1.3‡ (n=319)

n indicates the number of participants with measurements available in each subgroup. Values are mean±SD or geometric mean (5th–95th percentile interval). Reported values are standardized to the mean distribution in all participants of sex (if applicable), age, body mass index, 24-hour heart rate, plasma glucose, serum cholesterol, smoking, and drinking. Hypertension was a 24-hour ambulatory blood pressure of at least 130 mm Hg systolic or 80 mm Hg diastolic. Significance of the differences with normotension: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S2. Multivariable-Adjusted Indices of Target Organ Damage by Category of Daytime Hypertension

Measure of Target organ	Normotension	Isolated Diastolic Hypertension	Mixed Systolic and Diastolic Hypertension
Women			
Left ventricular mass index, g/m ²	87.7±15.3 (n=163)	90.6±15.3 (n=53)	92.8±15.5 (n=83)
Albumin-to-creatinine ratio, mg/mmol	0.60 (0.12–3.00) (n=270)	0.73 (0.14–3.81) (n=87)	0.88 (0.17–4.47)‡
Pulse wave velocity, m/s	7.5±1.3 (n=261)	7.6±1.3 (n=83)	8.3±1.3‡ (n=140)
Men			
Left ventricular mass index, g/m ²	92.0±14.5 (n=82)	92.3±13.6 (n=72)	97.0±14.0* (n=162)
Albumin-to-creatinine ratio, mg/mmol	0.37 (0.07-2.00) (n=150)	0.46 (0.10-2.20) (n=130)	0.58 (0.12-2.71)‡ (n=249)
Pulse wave velocity, m/s	7.4±1.2 (n=143)	7.6±1.1 (n=126)	8.1±1.1‡ (n=240)
All participants			
Left ventricular mass index, g/m ²	89.9±15.7 (n=245)	91.4±14.5 (n=125)	94.9±15.7‡ (n=245)
Albumin-to-creatinine ratio, mg/mmol	0.47 (0.09-2.36) (n=420)	0.58 (0.10-3.24)* (n=217)	0.71 (0.15-3.35)‡ (n=391)
Pulse wave velocity, m/s	7.4±1.2 (n=404)	7.6±1.2 (n=209)	8.2±1.2‡ (n=380)

n indicates the number of participants with measurements available in each subgroup. Values are mean±SD or geometric mean (5th–95th percentile interval). Reported values are standardized to the mean distribution in all participants of sex (if applicable), age, body mass index, daytime heart rate, plasma glucose, serum cholesterol, and smoking and drinking. Daytime hypertension was a daytime ambulatory blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic. Significance of the differences with normotension: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S3. Multivariable-Adjusted Indices of Target Organ Damage by Category of Nighttime Hypertension

Measure of Target organ	Normotension	Isolated Diastolic Hypertension	Mixed Systolic and Diastolic Hypertension
Women			
Left ventricular mass index, g/m ²	88.0±14.9 (n=155)	89.3±15.3 (n=81)	93.6±15.5* (n=74)
Albumin-to-creatinine ratio, mg/mmol	0.57 (0.12–2.74) (n=255)	0.71 (0.14–3.69)* (n=144)	0.98 (0.20–4.80)‡ (n=133)
Pulse wave velocity, m/s	7.5±1.3 (n=247)	7.7±1.3 (n=139)	8.4±1.2‡ (n=129)
Men			
Left ventricular mass index, g/m ²	93.0±14.0 (n=87)	93.6±13.9 (n=114)	96.7±14.3 (n=121)
Albumin-to-creatinine ratio, mg/mmol	0.40 (0.07–2.15) (n=152)	0.44 (0.08–2.33) (n=200)	0.59 (0.12–2.94)‡ (n=189)
Pulse wave velocity, m/s	7.6±1.2 (n=148)	7.6±1.1 (n=191)	8.1±1.2‡ (n=183)
All participants			
Left ventricular mass index, g/m ²	90.6±15.6 (n=242)	91.5±14.0 (n=195)	94.8±15.4* (n=195)
Albumin-to-creatinine ratio, mg/mmol	0.47 (0.10–2.31) (n=407)	0.56 (0.13–2.39)* (n=344)	0.76 (0.13–4.41)‡ (n=322)
Pulse wave velocity, m/s	7.6±1.2 (n=395)	7.7±1.3 (n=330)	8.2±1.2‡ (n=312)

n indicates the number of participants with measurements available in each subgroup. Values are mean±SD or geometric mean (5th–95th percentile interval). Reported values are standardized to the mean distribution in all participants of sex (if applicable), age, body mass index, nighttime heart rate, plasma glucose, serum cholesterol, and smoking and drinking. Nighttime hypertension was a nighttime ambulatory blood pressure of at least 120 mm Hg systolic or 70 mm Hg diastolic. Significance of the differences with normotension: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.